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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Antibody-Drug Conjugates in Glioblastoma Multiforme: Finding Ways Forward

Announcer:
Welcome to CME on ReachMD! This activity, Antibody-Drug Conjugates in Glioblastoma Multiforme: Finding Ways Forward, is provided by TOPEC Global and supported by an educational grant from AbbVie Inc.
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Your host is Dr. John Russell.

Dr. Russell:
Glioblastoma multiforme, or GBM, is a very aggressive brain malignancy. Even with our most up-to-date therapies, two-thirds of patients don't survive more than 2 years beyond their diagnosis. But new insights into the pathophysiology of this tumor are fundamentally changing our approaches to care, bringing new hope to patients and their providers. This is CME on ReachMD and I'm your host, Dr. John Russell. Joining me today is Dr. David Reardon, Professor of Medicine at Harvard Medical School, and Clinical Director of the Center for Neuro-Oncology at the Dana Farber Cancer Institute. We will be focusing on the role of EGFR and other molecular pathways in GBM pathophysiology, and review the latest clinical trial data obtained with agents targeting these pathways. Dr. Reardon, welcome to the program.

Dr. Reardon:
Yes, thank you very much.

Dr. Russell:
So doctor, let's start with the review of the current standard of care for patients with GBM. Can you describe the care pathway and how we've gotten to it?

Dr. Reardon:
Certainly, but before, it is important to note that the burden of glioblastoma multiforme (GBM) is rising globally. According to the WHO, the incidence of glioblastoma multiforme is growing, up to 2 to 3 per 100,000 people in the North America and Europe. In fact, according to a 2014 study of the Netherlands Cancer Registry, the proportion of glioblastoma rose between 1989–2010, while the proportion of anaplastic and unspecified astrocytoma decreased.
Even in Europe, there are regional variations in brain cancer incidence. A cancer registry found incidence of astrocytic tumors ranging from 3/100,000 in Eastern Europe to 5/100,000 in United Kingdom and Ireland. Overall, GBM incidence can be higher among Caucasians than other ethnic groups. We don't know why these variations exist, but certainly, genetic is one causing factor.
Our current standard of care for glioblastoma was established in 2005 and it includes a maximum safe resection, followed by radiation therapy, given in conjunction with daily temozolomide chemotherapy, and that's followed by 6 months of adjuvant temozolomide, typically given 5 days consecutively each month. That standard of care was established based on a randomized Phase III study that showed the addition of temozolomide chemotherapy during radiation, and then adjuvant after radiation therapy, improved survival compared to what had been the historical benchmark of radiation therapy alone, after surgery, by approximately 2.5 to 3 months; so a modest improvement. The study in the Netherlands found that the two-year survival rate of glioblastoma patients improved with the

introduction of combined chemoradiation, from 5% in the time period 1989–1994 to 15% in 2006–2010, with median survival increasing from 5.5 to 9 months.
So, the prognosis for GBM patients continue to be very glim, with a median survival time is 14.6 months from time of diagnosis. This low response to therapy seems similar across ethnic groups, though Asian/Pacific Islanders seem to have a better survival compared to the white population. Survival rate also may vary across European regions, with higher survival rate in Northern and Central Europe than in Eastern Europe and in UK and Ireland.
Since the Stupp regimen, there have been a number of efforts to further improve survival and outcome for newly diagnosed, as well as recurrent patients, and unfortunately, we've struggled with many of these studies and efforts. We have had some modest success, though. Recently, the alternating-electric-field device, known as Optune, was approved in the United States, and many other countries in the world, to be worn by patients with newly diagnosed glioblastoma, on the scalp, in conjunction with adjuvant post radiation temozolomide chemotherapy. Just recently, the FDA granted full approval of bevacizumab, a prototype of antiangiogenic therapy to be approved for use in the recurrent setting for glioblastoma patients.

Dr. Russell:
So doctor, we know that some important cellular and molecular pathways have recently been identified in the pathophysiology of this disease. What can you tell us about these pathways?

Dr. Reardon:
We know that a significant percentage of glioblastoma tumors aberrantly express growth factor receptors, such as the epidermal growth factor receptor, on the surface of the tumor cells. And these aberrantly expressed growth factor receptors act as accelerators, or drivers, that activate downstream signaling pathways such as the PI3-AKT pathway and the Ras-MAP kinase pathway in the vast majority of glioblastoma tumors, and these aberrantly activated pathways then lead to significant proliferation, diminished apoptosis, remarkable invasion in angiogenesis, the hallmark phenotypic features associated with glioblastoma tumors.

Dr. Russell:
So, what are the implications of these new understandings in terms of the therapies being investigated? So could we start with the EGFR targeted agents, since so many tumors carry this mutation?

Dr. Reardon:
Certainly. The epidermal growth factor receptor, we know in primary glioblastoma tumors, the vast majority of glioblastoma tumors, significantly upregulate the expression of EGFR, and we can find it on almost every glioblastoma tumor. Some of them have it upregulated remarkably, in fact, 30 to 40% of glioblastoma tumors actually have gene amplification, where we can find hundreds of copies of the EGFR gene within glioblastoma tumors. The exploitation of this knowledge and this aberrant signaling of EGFR in glioblastoma, however, has been challenging. We started off with monoclonal antibodies to block EGFR, and we know in lung cancer and colorectal cancer, some of these molecules have been quite successful. Unfortunately, they have not worked well in glioblastoma tumors, and at the same time, we turn to some of the small-molecule tyrosine kinase inhibitors like gefitinib and erlotinib that also have been quite successful in other EGFR-driven cancers, but unfortunately, these small-molecule inhibitors, we've discovered, don't penetrate the brain effectively.

Dr. Russell:
So, what else is being investigated?

Dr. Reardon:
Well, let me, maybe, provide a little bit more detail on the data related to the antibody-drug conjugate molecules that have really emerged and shown some promising results, somewhat surprising, to be honest, but encouraging results in glioblastoma patients. These molecules work by a novel mechanism where they bind effectively to the target epidermal growth factor receptor, but the actual killing of the tumor is related to a molecule conjugated to the antibody, a very potent toxin molecule, that's only released once the antibody has bound to the tumor cell. And once that antibody binds and releases the toxin, that cell, and only that cell, is killed by the guided missile, if you will, that the antibody-drug conjugate provides. So, this type of strategy has proven to be of significant benefit. We have randomized Phase II studies now and III studies that have been conducted in a recurrent setting, and an ongoing Phase III study called the INTELLANCE 1 study, a randomized placebo controlled study in newly diagnosed glioblastoma patients that are all going forward now, based on the preliminary data that's been accumulated to date. In that data, we saw the tumors, particularly those that have amplification of the EGFR gene, that approximately 25% of those patients had a radiographic response to the antibody-drug conjugate molecule ABT-414. Twenty-five percent, although that sounds like a small number and a minority of patients, the historical benchmark is less than 5%, so this is a significant improvement over what we've seen historically, and indeed, the durability of that benefit has also been encouraging, where we have a progression-free survival at 6 months' rate of about 30 to 40% of patients. And again, the historical benchmark is approximately 10%. So, these data are quite encouraging and certainly justify the further study,

including the Phase III studies ongoing for this exciting therapeutic and class of agents for glioblastoma.
In addition to the antibody-drug conjugates, there is a lot of interest in other important molecules therapeutics that may have an impact in this disease. There are ongoing studies looking at targeting the molecules responsible for disregulated cell-cycle progression such as CDK4 and 6 inhibitors, and some of those effectively penetrate the blood-brain barrier and they're being actively tested now in the clinic. We also are working with PARP inhibitors which have been shown, in some preclinical data, to significantly enhance the chemo-toxicity of temozolomide in MGMT methylated glioblastoma tumors, and that type of an approach, combining PARP inhibitor-based DNA repair blockade with chemotherapy with temozolomide. That's also being evaluated in advanced clinical trials. And finally, there's a significant interest in immunotherapy for glioblastoma tumors, as there is for many different types of cancers, with several ongoing studies looking at checkpoint-blockade molecules, targeting PD-1 and other checkpoint molecules, as well as a variety of different vaccine approaches that are being actively pursued for this disease.

Dr. Russell:
So doctor, with all these new approaches in mind, what changes do you see on the horizon for managing our patients with GBM?

Dr. Reardon:
Well, we clearly need to do more research and invest in these clinical trials and direct our patients to participate in the trials, and really determine if these promising therapeutics, such as the antibody-drug conjugates, such as the molecules targeting disregulated cell-cycle progression, or DNA repair, and the immunotherapy molecules can truly have an impact and improve outcome, raise the bar, for these very challenging tumors.

Dr. Russell:
So doctor, before you wrap up, are there any other takeaways or call to action you want to share on this subject?

Dr. Reardon:
My biggest plea would be to advocate for referrals of patients, with either newly diagnosed or recurrent glioblastoma, to centers conducting clinical trials and research, so these patients can participate, and hopefully have an improved outcome, and, at the same time, importantly, contribute to our ongoing efforts to improve outcome for all patients with these challenging tumors.

Dr. Reardon:
One other important advance that's moving forward for the field of glioblastoma is that we are utilizing novel clinical trial designs that utilize an adaptive basion approach, which are much more efficient, and allow us to integrate molecular genetic analyses of patients' tumors in real time, to therapeutic approaches that patients may be randomized to on these adaptive clinical trials. We have the first adaptive clinical trial design for glioblastoma patients ongoing, called the INSIGHT trial. That's being done in North America, led by us, the Dana Farber, here in Boston, and then an international effort called the AGILE trial that will include both newly diagnosed and recurrent patients that also is utilizing this adaptive approach and molecular genetic characterization of patients' tumors to direct to therapeutic options for those patients.
The 2016 WHO classification Acknowledges the use molecular parameters to establish brain tumor diagnoses.
The fact that the WHO recognizes the heterogenicity of brain tumors will surely help push for a more individualized approach to management at the global level.

Dr. Russell:
Well, with that, I'd like to thank Dr. Reardon for joining me to talk about the latest advances in GBM understanding and treatment approaches. Dr. Reardon, it was great having you on the show today.

Dr. Reardon:
My pleasure. Thank you very much.

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